(19) JAPANESE PATENT OFFICE (JP)

(12) Official Gazette for Unexamined Patent Applications (A)

(11) Japanese Unexamined Patent Application (Kokai) No. Hei 6-256156

(43) Disclosure Date: 13 September 1994

(51) Int.Cl.[5]	Ident. Symbols	Internal Office Nos.	FI	Technology Indication
A61K 7/48		9051-4C		
7/00		9164-4C		
	X	9164-4C		
	D	9164- 4C		
	K	9164-4C		
	C	9164-4C		

Request for Examination: Not yet requested Number of Claims: 1 FD (Total of 6 pages)
Continued on last page

(21) Application No.: Hei 5-67376

(22) Application Date: 4 March 1993

(71) Applicant: 591082421
Maruzen Pharmaceutical Co., Ltd.
14703-10 Mukai higashi-cho, Onomichi-shi, Hiroshima-ken

(72) Inventor: Katsuki Kogawa
c/o Maruzen Pharmaceutical Co., Ltd.
14703-10 Mukai higashi-cho, Onomichi-shi, Hiroshima-ken

(74) Agent: Ichiro Itai, Patent Attorney

(54) Title of the Invention: Skin Cosmetic

(57) [Abstract]

[Objective] To provide a novel skin cosmetic that can effectively prevent skin blackening and that is of superior safety.

[Structure] A skin cosmetic that contains glabridin and amino acids and that inhibits inflammation and melanin production and deposition in the skin that are produced by external stimulation such as ultraviolet rays, due to the synergic action of these essential constituents.

[Claim]

[Claim 1] A skin cosmetic characterized in that it contains glabridin and amino acids as its essential components.

[Detailed Description of the Invention]

[0001]

[Field of industrial use] This invention relates to a skin cosmetic that inhibits inflammation and melanin production and deposition in the skin that are produced by external stimulation such as ultraviolet rays and that can prevent erythema (sunburn), blackening of the skin, liver spots and freckles.

[0002]

[Prior art] In the final stage of the process of blackening of the skin, the black pigment melanin is produced as a result of tyrosine, which is an amino acid, being subjected to the action of tyrosinase. Accordingly, attempts have been made to prevent deposition of the pigment by applying various drugs, for example, glutathione and vitamin C, that inhibit the action of tyrosinase. However, these drugs are not necessarily satisfactory in terms of safety and efficacy on local application.

[0003] Because the causes and triggers of melanin production other than tyrosinase have been reported, including activation of melanocytes by ultraviolet rays, the involvement of various chemical mediators due to inflammation, the involvement of active oxygen that is produced by ultraviolet rays, and, further, the involvement of skin peroxides, it is difficult to sufficiently inhibit the deposition of melanin by application of drugs that only inhibit the action of tyrosinase.

[0004]

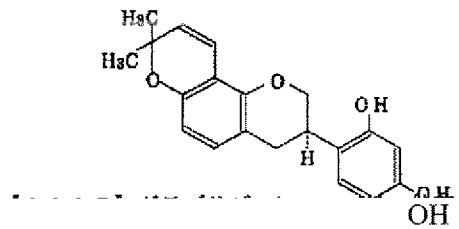
[Problems the action is intended to solve] The objective of this invention is to provide a novel skin cosmetic that can effectively prevent blackening of the skin in which the many factors described above are involved and that is also superior in terms of safety.

[0005]

[Means for solving the problems] The skin cosmetic of this invention is characterized in that it contains glabridin and amino acids as its essential constituents. It inhibits inflammation that is produced by external stimuli such as ultraviolet rays and production and deposition of melanin in the skin as the result of the synergic action of its essential constituents. Glabridin, which is one of the essential constituents of the cosmetic material of this invention, is a compound that has the structural formula indicated below. In nature, minute quantities are contained in Glycyrrizaglabra Linne var. (commonly called Russian-Afgan-Turkish licorice), which is a type of licorice.

[0006

[Chemical Formula 1]



[0007] It has been confirmed that glabridin has such pharmaceutical properties, such as antimicrobial action, antioxidant action, anticariogenic action and antiplasmin action. It is further known that it has a melanin production inhibiting action (Japanese Patent Application Early Disclosure No. Hei 1-311011 [1989]). However, the melanin production inhibiting action of glabridin that was confirmed was only for the case in which it was used alone. However, the effect when it is used in combination with other physiologically active substances such as amino acids is not known.

[0008] Glabridin is extracted from licorice. When it is used as the raw material for manufacture of the cosmetic material of this invention, the roots of the licorice or its aqueous extraction residue (for example, the residue when glycyrrhizin has been extracted) is extracted with an organic solvent. The extraction solvent can be a lower aliphatic alcohol such as methanol or ethanol, a lower aliphatic ketone such as acetone, an ether such as dioxane or ethyl ether, an halogenated hydrocarbon such as chloroform, an ester such as ethyl acetate, propyl acetate or butyl acetate, a hydrocarbon such as hexane or benzene and mixtures of two or more of these organic solvents. The licorice that is to be subjected to extraction treatment is immersed in approximately 5 to 15 times its volume of the above-described solvents and is allowed to stand at normal temperature or heated under reflux. The solvent is removed from the extraction solution and the extracted substance that is obtained usually contains on the order of 5 to 10% of glabridin. It can be used in unaltered form in the cosmetic material of this invention. However, a cosmetic material of a more superior use effect and of little coloration can be obtained by using a substance the purity of which has been increased by refining.

[0009] Refining of the extracted substance can be performed, for example, by a method in which it is treated by regular phase silica gel chromatography and reversed phase chromatography, after which it is crystallized from acetone. By this method, a pure glabridin product can be obtained comparatively easily. Purification can also be performed using any desired method of purification of organic compounds such as column chromatography with synthetic adsorbents and liquid-liquid countercurrent extraction.

[0010] Specific desirable examples of amino acids that can be contained in the skin cosmetic material of this invention together with glabridin include glycine, serine, valine, lysine, cystine, cysteine, alanine, leucine, isoleucine, glutamine, glutamic acid, tryptophan, arginine, asparagine, aspartic acid, threonine, methionine, phenylalanine, histidine, proline, n-methylserine, laminin, taurine, amino acid mixtures obtained by hydrolyzing proteins originating from animals or plants, amino acid mixtures obtained by fermenting microorganisms, and, in addition, amino acid mixtures obtained by extraction from yeast, marine algae and plant seeds. Two or more of these amino acids may be contained in the cosmetic material of this invention.

[0011] It is known that the above-described amino acids are present as important structural constituents of natural humectant factors in the skin and that they are decreased due to damage of the skin by external factors. It is known that amino acids play an important role in the maintenance of water in the stratum corneum of the skin, and, in turn, that they are closely related to maintenance of the health of the skin and to barriers to external irritation and that they have an extremely important action from a cosmetic standpoint. These actions occur synergically with the action of glabridin and have a role in the maintenance and formation of a desirable skin.

[0012] The suitable compounding quantity of glabridin in the skin cosmetic of this invention differs depending on the cosmetic material. However, ordinarily, it is approximately 0.001 to 10 wt%, and, preferably, approximately 0.01 to 1.0 wt%. The suitably compounding quantity of amino acids is approximately 0.002 to 5 wt%, and, preferably, approximately 0.01 to 2 wt%. Moreover, it is desirable that they be compounded to approximately 20 to 5000 wt% relative to the glabridin.

[0013] The cosmetic material of this invention can be any desired cosmetic material that makes advantageous use of the melanin production inhibiting action due to the combined use of glabridin and amino acid; for example, it can be in the form of toilet water, an emulsion, a cream, a pack, soap or body lotion. Structural constituents of cosmetic materials in addition to glabridin and amino acids such as, for example, oils and fats, surfactants, thickeners, pigments, fragrances, preservatives, ethanol and polyvalent alcohols, can be selected as desired in a range

that does not impair the actions of the other two components.

[0014]

[Working Examples]

[Example of manufacture of glabridin] 500 g of finely cut licorice root was immersed in 5 liters of ethyl acetate and was heated for 2 hours under reflux, with the constituent soluble in ethyl acetate being extracted. The same procedure was repeated for the extraction residue in which the extraction solution was separated, with a total of 9 liters of extraction solution being obtained. The solvent of the extraction solution was removed under decreased pressure and 13.1 g of extracted substance containing glabridin was obtained. Next, the extracted substance was dissolved in chloroform and was smeared on silica gel (Wako Gel C-300, manufactured by the Wako Junyaku Company, Ltd.), after which it was dried. This dried matter was laminated in a column that had been filled in advance with 1 kg of silica gel and was dissolved in a mixed solution of chloroform/methanol (30 : 1), the fraction containing glabridin then being collected. The solvent of this fraction was removed under decreased pressure and 5.8 g of solid matter was obtained, after which it was dissolved in a small quantity of methanol. It was then smeared on reverse phase silica gel (ODSG-3, product of the Mito Chemical Technology Research Laboratories) and was laminated on a column that had been filled in advance with 800 g of reverse phase silica gel. A mixed solution of water and acetonitrile (30 : 70) was passed through this column as the elution solvent and the fraction containing glabridin was collected. The solvent was removed from this fraction under decreased pressure, the solid matter (4.3 g) that was obtained was dissolved in 40 ml of acetone and the solution was allowed to stand for 3 days at 5°C. Crystals of the above-described purified glabridin were used as the glabridin in the following working examples.

[0015] Working Example 1

[Table 1] Toilet Water Formulations (Unit: wt%)

	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Surfactant	1	1	1	1
Ethanol	4	4	4	4
1,3-butylene glycol	4	4	4	4
Paraoxybenzoic acid ester	0.12	0.12	0.12	0.12
Fragrance	0.1	0.1	0.1	0.1
Glabridin	0.10	0.10	0.10	-
Amino Acid Mixture				
Casein hydrolysate	0.5	-	-	-
Seeweed extract	-	4	-	-
Auto-digested yeast	-	-	1	-
Mg ascorbate phosphate	-	-	-	3
Purified water	Remainder	Remainder	Remainder	Remainder

[0016] Note 1. Casein hydrolysate: Obtained by hydrolyzing dairy casein with protease and pepsin.

Seeweed extract: Extract obtained by adding 50 wt% of 1,3 butylene glycol to pulverized *Laminaria japonica* and allowing it to stand for 10 hours at room temperature while being stirred occasionally, after which it is subjected to clarifying filtration.

Auto-digested yeast: Powder obtained by auto-digestion of bread yeast, after which it was subjected to clarifying filtration and freeze-dried.

Note 2: Formulation 4 was a comparative example.

[0017] Toilet water was manufactured with the formulations in Table 1 above. In this case, the glabridin crystals obtained in the above-described Example of Manufacture were first dissolved in a mixed solution of ethanol and 1,3-butylene glycol, a surfactant (polyoxysorbitan monolaurate; 20 E.O), fragrances and paraoxybenzoic acid ester were added and dissolved, after which purified water and other constituents were added and the mixture was stirred to a homogeneous state.

[0018] Next, the use effectiveness of the above-described toilet water samples was tested by the method described below. Erythema inhibiting effect test method: The fur on the back of a brown guinea pig was shaved off and a 0.1% solution of oxolane was applied, and, after 30 minutes, irradiation of UVA 1J/cm^2 was performed. Immediately after irradiation, 5 sections of a size of 2 cm × 2 cm were determined in the irradiation site and the following preparations were applied to the respective sections.

A: The above described toilet water in unaltered form

B: Toilet water of the above-described formulations 1 to 3 from which the glabridin had been removed

C: Toilet water of the above-described formulations 1 to 3 from which the amino acid had been removed

D: Toilet water of the above-described formulations 1 to 3 from which both the glabridin and the amino acid had been removed

E: Toilet water of formulation 4

The erythema inhibiting effects after 24 hours was evaluated by observation with the unaided eye. (The color of skin that had not been subjected to PUVA treatment was taken as the reference color.)

[0019] Pigment deposition inhibiting effect test method: Sites in which deposition of pigment was found after one week in brown guinea pigs subjected to PUVA treatment in accordance with the erythema inhibiting effect test method were divided into five sections of sizes of 2 cm × 2cm, and any one of toilet waters A ~ E indicated previously were applied for 10 consecutive days, once in the morning and evening. The pigment deposition inhibiting effect after 10 days was evaluated by observation by the unaided eye (The color of skin that had not been subjected to PUVA treatment was taken as the reference color.)

[0020] The results are shown in Table 2 and Table 3. The toilet water of this invention, which contained both glabridin and the mixture of amino acids was found to have an effect in inhibiting erythema due to ultraviolet rays and a pigment deposition inhibiting effect markedly superior to that of toilet water (D), which did not contain either glabridin and a mixture of amino acids and to that of the comparative example toilet water (E) of formulation 4, in which magnesium ascorbate phosphate as used. The toilet water of this invention was also found to have a use effect superior to that of the application examples of toilet water that contained only one of glabridin and amino acid mixture (B and C). Inflammation and other skin lesions were not observed.

[0021]
[Table 2]

Basic formulation of toilet water	Erythema inhibiting effect
Formulation 1	Skin not subjected to PUVA treatment = A >> C = B >> D = E
Formulation 2	Skin not subjected to PUVA treatment = A >> C ≥ B >> D = E
Formulation 3	Skin not subjected to PUVA treatment = A >> C ≥ B >> D = E

[0022] [Table 3]

Basic formulation of toilet water	Pigment deposition inhibiting effect
Formulation 1	Skin not subjected to PUVA treatment = A >> C > E > B = D
Formulation 2	Skin not subjected to PUVA treatment ≥ A >> C > E > B = D
Formulation 3	Skin not subjected to PUVA treatment = A >> C > E > B = D

[0023] Working Example 2

Creams were manufactured with the formulations of Table 4. At the time of manufacture, raw materials of group (1) in the table were first dissolved at 70°C and were mixed with the raw materials (2), after which they were set to 78°C. Next, they were gradually added to raw materials (3), which had been heated to 75°C, while being stirred, with preliminary emulsification being effected. Following that, the materials were placed in an homogenizer and emulsification was completed. They were then cooled to 50°C, after which (4) was added and the material was cooled to 30°C. Formulation 8 was a comparative example.

[0024]

[Table 4] Cream Formulations (unit: wt%)

		Formulation 5	Formulation 6	Formulation 7	Formulation 8
(1)	Surfactant A	3.5	3.5	3.5	3.5
	Surfactant B	1.5	1.5	1.5	1.5
	Glabridin	0.05	0.05	0.05	-
(2)	Liquid paraffin	25.0	25.0	25.0	25.0
	Whale tallow	5.0	5.0	5.0	5.0
	Lanolin	5.0	5.0	5.0	5.0
	Cetanol	2.0	2.0	2.0	2.0
(3)	p-Oxybenzoic acid ester	0.2	0.2	0.2	0.2
	Glabridin	3.0	3.0	3.0	3.0

	Carboxyvinyl polymer	5.0	5.0	5.0	5.0
	Amino acid mixture	-	-	-	-
	Silk hydrolysate	0.5	-	-	-
	Wheat germ extract	-	2.0	-	-
	Soy bean hypocotyl extract	-	-	2.0	-
	Purified water	remainder	remainder	remainder	remainder
(4)	Fragrance	0.2	0.2	0.2	0.2

[0025] (Note 1) Surfactant A: Autoemulsified glycerol monostearate

Surfactant B: Sorbitan monostearate
carboxyvinyl polymer: 1% aqueous solution

[0026] Next, tests of the use effect of each of the above described creams were performed by the method described below. Pigment deposition inhibiting effect test method: The backs of brown guinea pigs were shaved, the shaved region was divided into four sections of 2 cm × 2 cm and UVB irradiation of 1 J/cm^2 per day was performed for 2 days. After 4 days, pigment deposition was observed. Therefore, either one of the following was applied once a day for 10 consecutive days.

A: The above described creams in unaltered form

B: Cream of the above described formulations from which only glabridin was removed

C: Cream of the above described formulations from which only amino acids were removed

D: Cream of formulation 7

After 10 days, the pigment deposition inhibiting effect was evaluated by the unaided eye (the color of skin that had not been subjected to UVB treatment being taken as the reference color).

[0027] Erythema inhibiting effect test method: Creams A ~ D indicated previously were applied to sections of the backs of brown guinea pigs that had been subjected to UVB treatment in accordance with the pigment deposition inhibiting effect test method and evaluations were made of the inhibiting effect on erythema after 24 hours by observation with the unaided eye (the color of skin that had not been subjected to UVB treatment being taken as the reference color).

[0028] The results are shown in Table 5 and Table 6. When the case in which creams of this invention containing glabridin and amino acid mixture were compared with cases of application of creams from which glabridin or amino acid mixture had been omitted, the inhibiting effect on erythema due to ultraviolet rays and pigment deposition inhibiting effect of the former were superior to the latter in both cases. In addition, inflammation and other skin lesions were not observed.

[0029]

[Table 5]

Basic formulation of cream	Pigment deposition inhibiting effect
Formulation 5	Skin not subjected to PUVA treatment = A >> C = B = D
Formulation 6	Skin not subjected to PUVA treatment ≥ A >> C = B = D
Formulation 7	Skin not subjected to PUVA treatment = A >> C = B ≥ D

[0030] [Table 6]

Basic formulation of cream	Erythema inhibiting effect
Formulation 5	Skin not subjected to PUVA treatment ≥ A >> C ≥ B ≥ D
Formulation 6	Skin not subjected to PUVA treatment ≥ A >> C ≥ B ≥ D
Formulation 7	Skin not subjected to PUVA treatment ≥ A >> C ≥ B ≥ D

[0031]

[Effect of the invention] As described above, the cosmetic material of this invention containing glabridin and amino acid mixture can effectively prevent inflammation of the skin due to ultraviolet rays and pigment deposition, with no undesirable side effects being found.

Continued from front page

(51) Int.Cl.[5]	Ident. Symbols	Internal Office Nos.	FI	Technology Indication
// C07D 493/04106	C	9165-4C		